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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/645,415      | 08/24/2000  | David G. Bermudes    | 8002-059-999        | 3240             |

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EXAMINER

SHUKLA, RAM R

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

|                 |               |              |                 |
|-----------------|---------------|--------------|-----------------|
| Application No. | 09/645,415    | Applicant(s) | BERMUDES ET AL. |
| Examiner        | Ram R. Shukla | Art Unit     | 1632            |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) Responsive to communication(s) filed on 28 May 2004.  
2a) This action is FINAL.      2b) This action is non-final.  
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) Claim(s) 2,5-14,16,26,40,49,52-61,63,100-188 and 2938 is/are pending in the application.  
4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.  
5) Claim(s) \_\_\_\_\_ is/are allowed.  
6) Claim(s) 2,5,6,12,14,16,26,29,30,36,38,40,49,52,53,59,61,63,105,118,131 and 144-155, 158-169 and 172-188 is/are rejected.  
7) Claim(s) \_\_\_\_\_ is/are objected to.  
8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) The specification is objected to by the Examiner.  
10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) All    b) Some \* c) None of:  
1. Certified copies of the priority documents have been received.  
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) Notice of References Cited (PTO-892)  
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: \_\_\_\_\_.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 7-11,13,31-35,37,54-58,60,100-104,106-117,119-130,132-143,156,157,170 and 171.

**DETAILED ACTION**

1. Applicants' response filed 05/28/04 has been received.
2. Claim 7-11, 13, 31-35, 37, 54-58, 60, 100-104, 106-117, 119-130, 132-141, 142, 143, 156, 157, 170 and 171 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species as discussed in the previous office action of 02-23-2004. Election was made **without** traverse in Paper No. 21.
3. Claims 2, 5, 6, 12, 14, 16, 26, 29, 30, 36, 38, 40, 49, 52, 53, 59, 61, 63, 105, 118, 131 and 144-155, 158-169 and 172-188 drawn to an attenuated tumor bacteria comprising an anti-angiogenic factor as the primary effector molecule, an animal as the organism from which the primary effector molecule is derived and a bacteriocin release factor as the secondary effector molecule are instant consideration as discussed in the previous office action of 02-23-2004.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2, 5, 6, 12, 14, 16, 26, 29, 30, 36, 38, 40, 49, 52, 53, 59, 61, 63, 105, 118, 131 and 144-155, 158-169 and 172-188 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record set forth in the previous office action of 2-23-04. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

***Response to Arguments***

Applicant's arguments filed 5/28/04 have been fully considered but they are not persuasive. In the first few pages applicants reiterate the office action of 2/23/04. On page 4 of the response applicants argue that applicants have designed a specific section of the specification- pages 41-47 for describing the secondary effectors. However, these arguments are not persuasive because the specification provides a laundry list of secondary effectors without any specific description. What is required is a specific description not a general list. The specification does not teach specific complete structure of a sufficient number of secondary effectors.

6. Claims 2, 5, 6, 12, 14, 16, 105, and 144-155 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an attenuated *Salmonella typhimurium* wherein said attenuated *Salmonella* comprises a first nucleic acid encoding a primary effector molecule wherein said primary effector molecule is endostatin and a second nucleic acid encoding a secondary effector molecule wherein said secondary effector molecule is BRP, does not reasonably provide enablement for any attenuated tumor targeted bacteria comprising any number of nucleic acids encoding any number of primary effector molecules and any number of secondary effector molecules for reasons of record set forth in the previous office action of 2/23/04. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 26, 29, 30, 36, 38, 40, 118 and 158-169 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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Claims 49, 52, 53, 59, 61, 63, 131 and 172-188 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

### ***Response to Arguments***

Applicant's arguments filed 5/28/04 have been fully considered but they are not persuasive. In pages 5-8, applicants reiterate the enablement rejection. Applicants, on page 8, first full paragraph, argue that the vaccine studies are irrelevant to the applicants claimed invention. Applicants argue:

"The tumor-targeted bacteria, unlike the vaccine vectors, act as both DNA delivering vector and effector molecule producer and do not require the transfer of their DNA molecule to mammalian cells."

However, these arguments are not persuasive because while the bacteria as vectors may not need lysis, they would pass through the animal circulation and therefore issues like attenuation etc. relevant to vaccination vectors would be relevant to any bacterial that is used as a vector. In fact, applicants cited Eisensntein et al in support of their arguments but this art teaches immunotherapy of cancer using attenuated salmonella (see the title). Applicants seem to be contradicting their own arguments. While Pawleke et al teaches tumor targeted Salmonella, it does not teach how to make and use a tumor targeted bacteria that has two exogenous nucleic acids, one which expresses a primary effector molecule and another which expresses a secondary effector molecule. Luo et al could not be used to support enablement for the instant application since it is a post filing art and it does not use the method taught in the specification. In fact this art also does not teach how to make and use a tumor targeted bacteria that has two exogenous nucleic acids, one which expresses a primary effector molecule and

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another which expresses a secondary effector molecule. Furthermore, all these three articles teach Salmonella not any other bacteria.

Applicants have submitted a copy of a 1.132 declaration by Dr. David Bermudes previously submitted in US 09/358,052. The declaration has been fully considered. However, the declaration is not sufficient to obviate the rejection in the instant application because while the declaration discusses Shigella flexneri, Listeria monocytogenes and Streptococcus agalactiae, the declaration does not teach whether these bacteria had any exogenous nucleic acid that encoded any primary or secondary effectors. In other words all these words would be working as vaccination vectors rather than delivery vector, the instant invention. Applicants in their argument seem to ignore this important limitation. Additionally, applicants seem to be arguing that their invention is not vaccination vector but then all the evidence they provide in support of their arguments are for vaccination.

Next applicants cited arts by Yu et al 2004 and Szalay 2003 which are post filing. Likewise applicants cite a US patent publication which has a filing date of 2002. However, these arts could not provide enabling support for the instant specification since they don't use the method taught by the specification.

Applicants have not provided any evidence that these arts used the method taught in the specification.

Next, regarding the anti-angiogenic proteins, applicants argue that the specification teaches these on pages, 5, 84, 85, however these sections are general descriptions and do not provide any specific teaching and guidance how to make any bacterial comprising nucleic acids that express angiogenic proteins wherein the bacteria when administered to an animal could provide targeted delivery to a tumor in the animal. Regarding in vivo treatment, again applicants reiterate the rejection and then argue:

In response, Applicants respectfully traverse the above ground of rejection. The Examiner is corrected that DNA transfer from bacteria to mammalian cells is very inefficient and unpredictable. Applicants would like to point out that the

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instant invention, using tumor-targeted bacteria for cancer treatment, **does not** involve DNA transfer between bacterial vectors and mammalian cells. Every bacterium contains the gene of interest and produces the said protein product by the bacteria.

However, these arguments are not persuasive since the issue of expression of the protein in the tumor is relevant even if the bacteria are not vaccine vectors.

Regarding the issue of route of administration, applicants did not provide any evidence rather they provide post filing arts by King et al (2004) and Nemunaitis et al (2003) which are post filing arts and there is no evidence that the methods used in the two articles are the same. Therefore, they cannot provide enabling support for the claimed invention.

7. No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

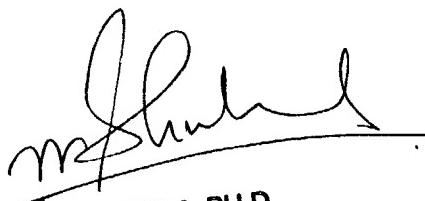
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ram R. Shukla, Ph.D.  
Primary Examiner  
Art Unit 1632



RAM R. SHUKLA, PH.D.  
PRIMARY EXAMINER